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VIA FACSIMILE - ORIGINAL BY POST

22nd December 2003

Dear Sirs,

International Patent Application No. PCT/GB02/00906
in the name of MOLECULARNATURE LIMITED *et al*
Our Reference: P58876F-WO/AVF/mes

1. Preamble

1.1 The following is responsive to the Written Opinion of the 10th October 2003 (due for reply, on extension, on the 10th February 2004).

1.2 Detailed substantive examination is hereby requested.

1.3 Issuance of a second written opinion is hereby requested in circumstances where a wholly favourable International Preliminary Examination Report is not issued directly.

2. Reply

2.1 Novelty

All of the claims require *inter alia* that:

- the *quality* of a *herbal medicine* be monitored *via* the use of a sample (the "first sample" of claim 1) of herbal medicine as starting material for the method;
- that a *polar* extract of a herbal medicine be *characterized* (see step (c) of claim 1).

The term *herbal medicine* is a term of art defined in the specification at page 6 in the following terms:

> ***The term herbal medicine is used herein to define a pharmaceutical composition in which at least one active principle is not chemically synthesized and is a phytochemical constituent of a plant. In most cases, this non-synthetic active principle is not purified, but present together with other phytochemicals with which it is associated in the source plant.***

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The term *quality*, as applied to herbal medicines, is defined in the specification at page 7 in the following terms:

> ***In this context, the term quality is used to define the overall fitness of the herbal medicament for its intended use, and may include for example the presence of one or more bioactive principles (at an appropriate concentration), the presence of one or more bioactive markers, a phytochemical profile which indicates the use of a particular source, condition, purity and an acceptable or unacceptable degree of contamination with undesirable supplements and/or contaminants.***

It is respectfully submitted that none of the cited prior art documents disclose either the use of a herbal medicine sample (as defined in the application) or the characterization of a polar extract thereof in a method of monitoring the quality of that herbal medicine.

Accordingly, it is submitted that the subject matter of the claims is clearly novel over the cited prior art.

2.2 Inventive step

As explained in the specification bridging pages 1 and 2, the present invention is concerned with the problem of *controlling the quality of herbal medicines*.

This is a growing and difficult problem. Although there is intense interest in the use of herbal remedies and a growing acceptance from healthcare companies and the medical profession that herbal medicinal products have value, quality control is difficult due to the complex nature and inherent non-uniformity of plant materials.

None of the cited prior art documents address this important problem.

Dealing with each item of prior art in turn:

2.2.1 WO 99/34810 (hereinafter D1)

Document D1 discloses the isolation of non-polar (*not* polar) extractives. The processes and methods described in this document are explicitly stated to effect the recovery of various non-polar compounds at high yield, purity and unaltered form for use in various forms of industry (see e.g. page 5, lines 7-8). Specifically, D1 discloses the use of an aliphatic-substituted polysaccharide gel matrix in a process of hydrophobic interaction chromatography "for the isolation, recovery and purification of non-polar extractives..." (see e.g. the Title). There is no teaching or suggestion that the processes be adapted and applied to the quality control of herbal medicines, or of the characterization of polar extracts for this (or any other) purpose.

Accordingly, it is submitted that D1 falls within an entirely different technical field to that of the present invention and is directed to a fundamentally different problem. It is therefore respectfully submitted that this document is not germane to an assessment of the inventiveness of the quality control methods of the present invention, either alone or in combination with any other cited document.

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2.2.2 Abidi (2001) (hereinafter D2)

Document D2 discloses the analysis of a particular class (sterols) of non-polar (*not* polar) extracts. The processes described in this document are explicitly stated to address an "the increasing public interest in the cholesterol-reducing capacity of phytosterols" and the "impetus to review existing chromatographic methods" generated thereby (see page 176, closing paragraph of section 1). The extracts analysed are non-polar (see section 2.1 at page 177), a corollary of the non-polar nature of the analytes of interest (sterols). There is no teaching or suggestion in D2 that the processes be adapted and applied to the quality control of herbal medicines, or of the characterization of *polar* extracts for this (or any other) purpose. Indeed, the entire teaching of D2 is narrowly confined to the analysis of non-polar sterol components (principally those present in vegetable oils).

Accordingly, it is submitted that D2 falls within an entirely different technical field to that of the present invention and is directed to a fundamentally different problem. It is therefore respectfully submitted that this document is not germane to an assessment of the inventiveness of the quality control methods of the present invention, either alone or in combination with any other cited document.

2.2.3 Janos (2003) (hereinafter D3)

Document D3 was published after the priority date of the present invention. Since the content of the priority document (GB0205186.0) is substantially identical to that of the international application as filed, it is submitted that all claims are entitled to the priority date of the 6th March 2002. Accordingly, it is submitted that D3 is not available as prior art in respect of the subject matter claimed.

Without prejudice to the generality of the above observations and argument, it is further observed that D3 is confined to the analysis of humic substances, defined as "ubiquitous natural materials occurring in huge amounts in soils, sediments and waters as a product of the chemical and biological transformation of animal and plant residues" (see Introduction, first paragraph, page 2). There is no teaching or suggestion in D3 that the processes be adapted and applied to the quality control of herbal medicines, or of the characterization of *polar* extracts of herbal medicines for this (or any other) purpose. Indeed, the entire teaching of D3 is narrowly confined to the analysis of humic substances.

Accordingly, it is submitted that D3 falls within an entirely different technical field to that of the present invention and is directed to a fundamentally different problem. It is therefore respectfully submitted that this document is not germane to an assessment of the inventiveness of the quality control methods of the present invention, either alone or in combination with any other cited document.

2.2.4 EP0886143 (hereinafter D4)

Document D4 is confined to the screening of compound libraries involving the capture and release of compounds with affinity for a target receptor: specifically, the target receptor is immobilised, compounds are presented and the actives bind. After removal of unbound compounds, ligands are displaced and ultimately characterised. There is no teaching or suggestion that the processes be adapted and applied to the quality control of herbal medicines, or of the characterization of polar extracts for this (or any other) purpose.

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Accordingly, it is submitted that D4 falls within an entirely different technical field to that of the present invention and is directed to a fundamentally different problem. It is therefore respectfully submitted that this document is not germane to an assessment of the inventiveness of the quality control methods of the present invention, either alone or in combination with any other cited document.

3. Conclusions

The invention as claimed is both novel and inventive over D1 to D4.

Issuance of a wholly favourable IPER or a further Written Opinion setting out any remaining objections in more detail is requested in the light of the above arguments and observations.

Yours faithfully,
FRY HEATH SPENCE

Alan V. Fry